a. contacting one or more test agents with a cell that expresses a wild-type patched protein and identifying test agents that [change] decrease the level of [patched-dependent intracellular] hedgehog signal transduction relative to the absence of test agent;

b. contacting test agents identified in step (a) with a cell having a patched loss-of-function phenotype and selecting those test agents that reverse at least in part the patched loss-of-function phenotype; and

c. preparing a formulation including a test agent that inhibits the growth of cells selected in step (b) and a pharmaceutically acceptable diluent.

74. (**Twice Amended**) The method of claim 61 or 62, further comprising preparing a formulation including an agent which [affects patched-dependent] decreases hedgehog signal transduction and a pharmaceutically acceptable excipient.

76. (**Twice Amended**) The method of claim 63, further comprising preparing a formulation including an agent which [affects patched-dependent] decreases hedgehog signal transduction and a pharmaceutically acceptable excipient.

REMARKS

Claims 61-77 constitute the pending claims in the present application. Applicants respectfully request reconsideration in view of the following remarks. Applicants thank the Examiner for courtesies extended during a telephonic interview on March 7, 2002.

1. Claims 62 and 72-75 are rejected under 35 U.S.C. 112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants maintain the arguments of record with regard to possession of the previously claimed subject matter. Nevertheless, to expedite prosecution of the present application, Applicants have amended the claims. Such amendments

are not in acquiescence of the previous rejection, and Applicants reserve the right to prosecute claims of similar or differing scope. Reconsideration and withdrawal are respectfully requested.

2. Claims 61-77 are rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, particularly for failing to enable for methods of identifying agents which are useful for treating an animal having a disorder characterized by loss of function of a *patched* gene. Applicants traverse this rejection to the extend that it is maintained over the amended claims.

Applicants have provided an extensive discussion of the role of the patched tumor suppressor in hedgehog signaling, including the link between mutations in patched and proliferative disorders in both mouse models and human patients (see, for example, page 36, line 29-page 37, line18; page 41, table 2). Given the role of patched and hedgehog signaling in a wide range of proliferative disorders, Applicants have disclosed prophetic examples which include the use of the subject methods to identify agents which decrease cell proliferation. The standard for enablement is not whether Applicants have reduced every embodiment encompassed by the claims to practice, but whether one of skill in the art could practice the claimed invention without undue experimentation in light of the disclosure and the state of the art. Certainly, given the well established role of patched as a tumor suppressor, and the involvement of hedgehog signaling in a wide range of proliferative disorders, one of skill in the art would be able to practice the claimed methods in light of the disclosure, and would have a reasonable expectation of success of identifying agents which affect cell proliferation.

The Examiner is reminded that in accordance with MPEP 2164.06, the fact that the amount of experimentation required is extensive or time consuming does not make such experimentation undue. "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). "An extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977).

The claims are additionally rejected for allegedly failing to enable for in vivo methods of treatment. Once again, Applicants have presented a prophetic example of an embodiment of the invention, and the standard for evaluating this embodiment is whether one of skill could determine whether the embodiment is operative or inoperative. Applicants have provided an animal model which can be readily used by one of skill in the art to hone in on the identified agents likely to have therapeutic potential before initiating further in vivo human experiments. For example, Applicants have provided patched "knock-out" mice (homozygous patched loss-of-function mice, pages 34-46), as well as patched heterozygous mice which have a phenotype which includes medulloblastomas and skeletal defects (page 36-38). One of skill can readily use cells and tissue from these animals to test the lead compounds identified by the methods of the present invention.

Applicants once again refer the Examiner to PCT application WO01/26644 (previously provided) which demonstrates that, following the teachings of the present application, one of skill could (and did) identify compounds that decrease hedgehog signal transduction. Applicants specifically refer to three assays presented in WO01/26644: a ptc-null assay (page 123, line 4-page 124, line 16), a murine BCC skin punch assay (page 128, line 15-page 129, line12), and a human BCC explant culture assay (page 129, line 15-page 130, line 11).

The ptc-null assay demonstrates that a test compound (compound D) decreases hedgehog signaling in cells lacking a functional patched gene. A decrease in hedgehog signaling is shown by RT-PCR analysis of the gli-1 transcription factor known in the art to be activated by hedgehog signaling. Applicants note that such a ptc-null cell line can be readily used to screen any number of test compounds for the ability to decrease hedgehog signaling in a ptc loss-of-function background.

WO01/26644 further demonstrates that test compound D inhibits hedgehog signaling in both a mouse and a human BCC skin punch assay (page 128, line 15-page 130, line 11). The mouse model involves the induction of BCC-like lesions in ptc heterozygous mice. These mice are irradiated three times weekly for six months, and the BCC lesions are the result of loss-of heterozygosity of the functional ptc allele. Such a mechanism is well known in the art, and is supported by the originally filed specification (page 8, lines 19-29; page 38, lines 3-9).

Accordingly, this provides an effective animal model for testing or screening for compounds which decrease hedgehog signaling in a patched loss-of-function background. Additionally, WO01/26644 demonstrates similar results using human BCC samples.

Applicants point out that the results presented in WO01/26644 demonstrate that test compounds can be evaluated for the ability to decrease hedgehog signal transduction in a patched loss-of-function background, as evidenced by the expression of the transcription factor gli-1. Furthermore, the results indicate that such compounds can be readily evaluated for the ability to decrease hedgehog signal transduction. Applicants point that contacting the cells with compound D not only decreases expression of gli-1 (decrease in hedgehog signal transduction), but also decreases the size of the BCC lesions. This indicates that these methods can also be used to identify compounds which affect cell proliferation.

Accordingly, Applicants contend that this study demonstrates that the disclosure provides enablement for the full scope of the invention. Given the disclosed methods, one of skill in the art would have been able to identify a compound which decreases hedgehog signal transduction, and use that compound to decrease cellular proliferation by following the teachings of the specification, in light of the level of skill in the art, without undue experimentation.

In accordance with MPEP 2164.02, "if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate." Applicants further point out that "a rigorous or an invariable exact correlation is not required." As stated in Cross v. Iizuka, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985). "[B]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed in vitro utility and an in vivo activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence."

The Office Action cites the unpredictability in predicting the ultimate efficacy of drugs for the treatment of diseases. However, in accordance with MPEP 2107.02 (V), "it is improper for Office personnel to request evidence of safety in the treatment of humans, or regarding the degree of effectiveness." Although the process of ultimately identifying drugs which can be brought *to market* is a long, arduous, and perhaps unpredictable one, evaluating drugs on this

basis is the responsibility of the FDA. "The office must confine its review of patent applications to the statutory requirements of the patent law. Other agencies of the government have been assigned the responsibility of ensuring conformance to standards established by statute for the advertisement, use, sale or distribution of drugs." (MPEP 2107.02 (V)). Whether an agent identified by the methods of this invention is ultimately suitable as a therapeutic *product* is not the standard for the enablement of the full scope of these claims.

Applicants maintain that the specification, in light of the level of skill in the art, enables one of skill to practice the claimed invention without undue experimentation. The specification provides extensive teachings that the patched tumor suppressor and hedgehog signaling are involved in a range of proliferative disorders, and thus one of skill in the art would have a reasonable expectation of success of using the subject methods to identify agents which decrease cellular proliferation. The standard for the enablement of the scope of the claims is not whether Applicants have reduced to practice every embodiment of the claimed invention, but whether Applicants have provided sufficient guidance such that one of skill in the art can reduce the embodiment to practice using the disclosure and the level of skill in the art. Applicants contend that the level of skill in the art is high, and that even if the amount of experimentation necessary to practice the invention may be extensive, such experimentation is routine. Applicants contention that the claims are enabled throughout their scope is further supported by Exhibit 1 which demonstrates that one of skill **can** use the disclosure to identify lead compounds which can be further tested in in vitro and animal models for efficacy in affecting proliferation. Furthermore, in accordance with the MPEP, Applicants need not demonstrate that compounds identified using the claimed methods will ultimately gain FDA approval. Accordingly, Applicants have satisfied the standards for the enablement of the claimed subject matter. Reconsideration and withdrawal of this rejection is requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned

at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,

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